CLAIMS:

1. A method for the preparation of an immunoglobulin Fv fragment, comprising
   a. culturing recombinant microbial cells having nucleic acid encoding the Fv fragment comprising an immunoglobulin heavy chain variable region and an immunoglobulin light chain variable region, said light or heavy chain also comprising an unpaired cysteinyl residue C-terminal to the heavy chain variable region or the light chain variable region, whereby said culturing results in expression of said nucleic acid and secretion of the fragment into the periplasm of the microbial cells, and
   b. revovering the Fv fragment, wherein the recovered fragment has the cysteinyl residue present as a free thiol.

2. A method for the preparation of a Fab' antibody polypeptide having at least one cysteine in a hinge region of the antibody present as a free thiol (Fab'-SH), comprising the steps of:
   a. expressing nucleic acid encoding an immunoglobulin amino acid sequence comprising Fab' in microbial host cells transformed with a vector comprising said nucleic acid operably linked to control sequences which direct the secretion of Fab' to the periplasmic space of the host cell;
   b. permitting the formation of Fab'-SH within the host cell; and
   c. revovering the Fab'-SH from said host cell.

3. The method of claim 2 wherein said Fab'-SH is not exposed to reducing conditions during step c.

4. The method of claim 2 wherein said Fab'-SH has only one hinge region cysteine.

5. The method of claim 4 wherein said Fab'-SH is recovered with the hinge cysteinyl thiol maintained in protonated form.

6. The method of claim 2 wherein a metal ion chelating agent is present during the culturing of the transformed cell.

7. The method of claim 2 wherein a metal ion chelating agent is present during the recovery of said Fab'-SH.

8. The method of claim 2 wherein a protease inhibitor which inactivates or inhibits host cell proteases is present during the recovery of said Fab'-SH.

9. The method of claim 8 wherein the protease inhibitor is selected from the group consisting of: EDTA; phenyl-methylsulfonyl fluoride (PMSF); leupeptin; pepstatin and benzamidine.

10. The method of claim 2 wherein said Fab'-SH is recovered by freeze-thawing the host cells and subjecting the host cells to osmotic shock in the presence of lysozyme.

11. The method of claim 2 wherein Fab' comprises the C-terminal amino acid sequence Cys Ala Ala.

12. The method of claim 2 wherein said microbial host cells comprise E. coli cells.

13. A method for the preparation of $F(ab')_2$ comprising the steps of:

a. expressing nucleic acid encoding a first Fab', said first Fab' being capable of binding a first epitope, in a microbial host cell, having a periplasmic space, transformed with a vector comprising the nucleic acid operably linked to

control sequences which direct the secretion of said first Fab' to the periplasmic space of the host cell;

b. expressing nucleic acid encoding a second Fab', said second Fab' being capable of binding a second epitope, in a microbial host cell, having a periplasmic space, transformed with a vector comprising the nucleic acid encoding the second Fab' operably linked to control sequences which direct the secretion of said second Fab' to the periplasmic space of the host cell;

c. permitting the formation of first and second Fab'-SH within the periplasmic spaces of said host cells;

d. recovering said first and second Fab'-SH from the periplasmic spaces of said host cells; and

e. forming a covalent bond between the cysteinyl free thiols of said first and second Fab'-SH to form bivalent $F(ab')_2$.

14. The method of claim 13 wherein said covalent bond is a disulfide bond.

15. The method of claim 14 wherein the bond formation between the first and second Fab'-SH comprises the following steps:

a. reacting the first Fab'-SH with (i) 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) to form a thionitrobenzoate derivative Fab'-TNB or (ii) a bifunctional maleimide;

b. directly coupling said Fab'-TNB or maleimidated Fab' to the second Fab'-SH to form a $F(ab')_2$; and

c. recovering said $F(ab')_2$.

16. The method of claim 13 wherein the epitopes bound by the two Fab' are located on the same antigen.

17. The method of claim 13 wherein the epitopes bound by the two Fab' are located on different antigens.

18. The method of claim 13 wherein the microbial host cell is provided in a cell culture, and each Fab' is present in the culture at levels in excess of about 1 gram/liter.

19. The method of claim 13 wherein each Fab' comprises complementarity determining region amino acids from a non-human immunoglobulin and amino acids from a human immunoglobulin.

20. The method of claim 19 wherein the amino acid sequences are obtained from IgG.

21. $F(ab')_2$ made by the method of claim 13.

22. A method for high yield production of an immunoglobulin polypeptide comprising culturing a host cell transformed with nucleic acid encoding an immunoglobulin polypeptide under the transcriptional control of an inducible promoter/operator system wherein the promoter/operator system is subsequently induced, thereby resulting in polypeptide levels in the cell culture of greater than about 1 gram of polypeptide per liter of cell culture.

23. The method of claim 2 wherein said Fab'-SH has more than one hinge region cysteine.

24. The method of claim 2 wherein the light and heavy chains of said Fab' are not covalently bound.

Add A2 & C2